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Fetal hormonal programming of sex differences in depression: linking women's mental health with sex differences in the brain across the lifespan

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Women's health has traditionally been thought of in the realm of reproductive health, and that includes women's mental health (i.e., perinatal psychiatry). However, we now know there are significant sex differences in many chronic diseases, including brain disorders. Thus, understanding the causes of sex differences in disorders of the brain, within and outside of reproduction, is critical to understanding women's mental health and healthcare needs. In order to accomplish this, it is necessary for neuroscience to adopt a "sex-dependent" and/or "sex-specific" lens on investigations of the brain. In this review, we make the case for depression, which has among the largest sex differences in disorders of the brain.

Major depressive disorder (MDD) recently became the number one cause of disability worldwide (Murray and Lopez, 1997; Ustun et al., 2004; World Health Organization, 2012). Importantly, the incidence of MDD in women is twice that of men (Kessler, 2003; Kendler et al., 2006), and thus understanding its pathophysiology has widespread implications for attenuation and prevention of disease burden, particularly in women. Over 40 years of research implicate hormonal dysregulation underlying mood disorders (Board et al., 1956; Gibbons and McHugh, 1962; Coplan et al., 2000; Brouwer et al., 2005; Kurt et al., 2007; Barim et al., 2009),

particularly involvement of hypothalamic-pituitary-adrenal (HPA) and HP-gonadal (HPG) axes (Board et al., 1956; Gibbons and McHugh, 1962; Plotsky et al., 1998; Young and Korszun, 2002; Swaab et al., 2005). Central dysregulation of hormonal axes can precede MDD onset suggesting a role for hormonal abnormalities in female MDD vulnerability. Ours and others' work demonstrated that the vulnerability for sex-dependent risk for MDD begins in fetal development (McClellan et al., 2010; Goldstein et al., 2011; Zuloaga et al., 2012a,b; Carbone and Handa, 2013; Seney et al., 2013). Despite these findings, a number of confounds (state vs. trait, treatment, age, and recurrence) present challenges to elucidating the contribution of hormonal or genetic sex (Seney et al., 2013) to the co-occurrence of hormonal dysregulation and mood disorders.

HPA AXIS IMPLICATED IN MDD

A central role for the HPA axis in MDD was initially expressed clinically. Depressive symptoms/MDD co-occurred with endogenously elevated cortisol (Sonino et al., 1998) or exogenously administered corticosteroids (Kelly et al., 1980; Ling et al., 1981). Studies demonstrated elevated levels of cortisol in plasma, CSF, and 24-h urine samples, high CSF corticotrophin releasing hormone (CRH) levels, blunted responses to CRH

administration, and non-suppression of cortisol secretion on the dexamethasone suppression test in MDD (Carroll et al., 1976, 1981; Jarrett et al., 1983; Nemeroff et al., 1984; Halbreich et al., 1985; Holsboer et al., 1985; Banki et al., 1987; Evans and Nemeroff, 1987; Rubin et al., 1987; Heim et al., 2001; Newport et al., 2003; Raison and Miller, 2003). HPA axis dysregulation was related to age (Nelson et al., 1984a,b; Bremner et al., 2007), depression subtype (Brouwer et al., 2005), recurrence (Poor et al., 2004), and treatment response, albeit inconsistently (Nemeroff et al., 1991; De Bellis et al., 1993; Veith et al., 1993; McKay and Zakzanis, 2010). One potential confound was whether HPA axis dysregulation reflected clinical state or diagnostic trait. A meta-analysis of >1500 individuals (Vreeburg et al., 2009), demonstrated that hypercortisolemia, present in currently depressed individuals (Trestman et al., 1993; Ahrens et al., 2008), persisted after recovery (Vreeburg et al., 2009), while other studies reported abnormal blunted cortisol response to stress in recurrent cases (Ahrens et al., 2008). In either case, findings suggested HPA dysregulation as a trait. In contrast, some studies showed resolution of hypercortisolemia with treatment (Vythilingam et al., 2004; Lok et al., 2012), arguing that HPA dysregulation was due to clinical state. Elevated baseline

cortisol, enhanced CRH sensitivity, and lack of responsivity to dexamethasone suppression also predicted relapse vulnerability and sustained remission (Zobel et al., 1999; Appelhof et al., 2006; Ising et al., 2007). Despite this evidence, HPA-axis targeted treatments are not reliably effective in MDD, although show some success as anti-depressant adjuncts (Jahn et al., 2004) or improvement of cognitive deficits (Young et al., 2004).

Despite substantial data supporting sex differences in HPA functioning during stress in healthy populations (Kudielka and Kirschbaum, 2005; Goldstein et al., 2010) and MDD women (Holsen et al., 2011, 2013), reports of sex differences in the HPA axis and MDD are inconsistent. Men, but not women, with MDD demonstrated increased ACTH pulsatility (Young et al., 2007a) and elevated cortisol compared with non-depressed men and women (Bremner et al., 2007; Hinkelmann et al., 2012). However, depressed women vs. men (Poor et al., 2004) and non-depressed women (Young and Altemus, 2004; Chopra et al., 2009) also expressed hypercortisolemia. Study inconsistencies may be related to timing of cortisol assessments or may reflect methodological confounds, such as age of study subjects (e.g., post-menopausal women differ from premenopausal women and thus sex differences differ), chronicity of illness (e.g., sustained illness may produce blunted cortisol response rather than hypercortisolemia), or low statistical power to detect sex differences which may vary in effect size, depending on characteristics of the sample (details next paragraph). Further, genetic background likely affects HPA axis dysregulation, as demonstrated in studies showing increased ACTH and cortisol in males (but not females) homozygotic for the *alpha*(2)-adrenoreceptor gene and females (but not males) homozygotic for the *beta*(2)-adrenoreceptor gene (Haefner et al., 2008). Collectively, these findings offer initial evidence of sex differences in the role of HPA axis in MDD pathophysiology and emphasize the importance of considering genetic variation in HPA axis-associated genes.

Some studies report no effect of sex on HPA axis deficits in MDD (Carroll et al.,

1976; Nelson et al., 1984b; Dahl et al., 1989; Maes et al., 1994; Deuschle et al., 1998; Brouwer et al., 2005; Vreeburg et al., 2009), although some of these studies were not designed initially to investigate sex differences, introducing potential confounds, such as: oversampling women (thus small samples of men) and low statistical power to test for sex differences (Brouwer et al., 2005; Young et al., 2007a; Vreeburg et al., 2009; Hinkelmann et al., 2012); lack of control for use of oral contraceptives or estrogen-replacement therapy (Brouwer et al., 2005) affecting plasma cortisol levels (Kirschbaum et al., 1999); and disregard for menstrual cycle phase or menopausal status during data collection. These confounds present significant challenges to understanding study inconsistencies on sex differences in HPA-MDD associations and their implications for women's mental health.

HPG AXIS IMPLICATED IN MDD

Post-puberty adolescence is a key period during which sex differences in MDD begin to emerge, initially during ages 13–15, with the largest increase in late adolescence (e.g., Hankin et al., 1998). However, few studies have focused on understanding why the higher rate of MDD in girls than boys is initiated during this period. This is unfortunate since puberty is an important critical period for brain plasticity likely arising from differential flooding of the brain with gonadal hormones (Schulz et al., 2009), and further sexual differentiation of the brain as the prefrontal cortex fully develops during ages 18–22 years. Evidence for HPG axis-MDD associations also came from studies of polycystic ovarian syndrome (Himelein and Thatcher, 2006) and literature relating women's reproductive biology to mood fluctuations and depression (Steiner, 1992; Bloch et al., 2000; Payne, 2003; Angold and Costello, 2006; Young et al., 2007b; Graziottin and Serafini, 2009; Brummelte and Galea, 2010). Although there has been less examination of HPG deficits in MDD in men, lower testosterone has been reported (Schweiger et al., 1999; Seidman et al., 2001). HPG dysregulation in MDD has included androgens (Baischer et al., 1995; Rubinow and Schmidt, 1996; Schweiger et al., 1999; Seidman et al., 2001; Weiner et al., 2004), estrogens (Young

et al., 2000), and pituitary function (Daly et al., 2003). Women with persistent MDD had two times the risk of earlier perimenopausal transition, higher FSH, and lower estradiol levels, suggesting an early decline in ovarian function (Young et al., 2000; Harlow et al., 2003). Further, depressive symptom severity was associated with low estradiol levels (Baischer et al., 1995).

HPA-HPG INTERACTIONS IMPLICATED IN MDD

Dysregulation of HPA and HPG axes interact in MDD. Low levels of estradiol with unopposed progesterone in premenopausal MDD was associated with decreased inhibitory feedback on HPA function during stress, resulting in elevated cortisol in MDD compared to healthy women or men (Young and Altemus, 2004). Transient dysregulation of HPA axis during the luteal menstrual phase was reported in premenstrual syndrome (Rabin et al., 1990; Roca et al., 2003). Further, using functional MRI, our group showed *hypo*activity in stress-responsive regions in *premenopausal* MDD women was significantly associated with decreased estradiol and increased progesterone levels during the late follicular menstrual phase (Holsen et al., 2011). In *perimenopausal* MDD women, these brain regions were associated with *hyper*cortisolemia and *hyper*activity (Holsen et al., 2013). These imaging studies suggest a complex interplay between HPA and HPG axes, dependent on age and cycle timing. From a brain circuitry point of view, MDD involves hypothalamic (HYPO) nuclei (paraventricular and ventromedial), central amygdala (AMYG), hippocampus (HIPPO), anterior cingulate, medial and orbital prefrontal cortices (ACC, mPFC, OFC) (Dougherty and Rauch, 1997; Mayberg, 1997; Drevets et al., 2002; Sheline et al., 2002; Rauch et al., 2003), regions dense in glucocorticoid and sex steroid hormone receptors (MacLusky et al., 1987; Clark et al., 1988; Handa et al., 1994; Kawata, 1995; Tobet and Hanna, 1997; Donahue et al., 2000; Östlund et al., 2003). These regions develop in sex-dependent ways, in part driven by gonadal hormones. There is now a substantial body of functional imaging work relating regulation of mood with endocrine

function, e.g., Goldstein et al., 2005, 2010; Protopopescu et al., 2005; Amin et al., 2006; Stark et al., 2006; Dreher et al., 2007; Wang et al., 2007; Pruessner et al., 2008; van Wingen et al., 2008a,b, 2009; Root et al., 2009; Andreano and Cahill, 2010.

SHARED MOOD AND ENDOCRINE CIRCUITRY ARE SEXUALLY DIMORPHIC

In vivo imaging and postmortem studies demonstrated sex differences in brain volumes (or nuclei) of regions associated with MDD, although there is little work focused on sexual dimorphisms in MDD *per se*. In healthy women compared with men, relative to cerebrum size, findings supported greater relative volumes of HIPP (Filipek et al., 1994; Giedd et al., 1996; Murphy et al., 1996; Goldstein et al., 2001), ACC (Paus et al., 1996; Goldstein et al., 2001), and OFC (Goldstein et al., 2001). In men, there are relatively greater volumes of AMYG (Giedd et al., 1996; Goldstein et al., 2001), HYPO (Swaab and Fliers, 1985; Allen et al., 1989; Goldstein et al., 2001), and paracingulate gyrus (Goldstein et al., 2001; Paus et al., 1996). Recently, a number of new studies have emerged further characterizing sex-dependent circuitry (Ruigrok et al., 2013), connectivity (Ingallhalikar et al., 2014), and potential mechanisms (Raznahan et al., 2010; Kang et al., 2011; Goldstein et al., 2013; Lenz et al., 2013; Nguyen et al., 2013). Developmental pathways involve, in part, gonadal hormone regulation, seen in model animal (McEwen, 1983; Simerly et al., 1990; Tobet et al., 1993, 2009; O'Keefe et al., 1995; Park et al., 1996; Tobet and Hanna, 1997; Gorski, 2000; Chung et al., 2006) and human (Goldstein et al., 2001; Raznahan et al., 2010) development. In fact, preclinical studies demonstrated lasting effects of prenatal adverse events on HPA axis and noradrenergic stress systems (Takahashi et al., 1992; Weinstock et al., 1992; Vallee et al., 1997; Weinstock, 1997). These included hypothalamic and hippocampal structure and function (Takahashi et al., 1992; Matsumoto and Arai, 1997; Weinstock, 1997), with effects that occurred through programming a "hyperactive" system more vulnerable to adult depressive and anxiety-like behaviors and autonomic nervous system deficits, among others (Weinstock et al., 1992; Henry et al., 1994; Barker,

1995; Seckl, 2001; Majdic and Tobet, 2011; Zuloaga et al., 2011; Carbone et al., 2012). Analogous to timing of these events in animals, mid-to-late gestation in humans is a particularly vulnerable time for the impact of prenatal events on sex-dependent brain development (Tobet et al., 2009; Majdic and Tobet, 2011; Zuloaga et al., 2011; Carbone et al., 2012), and recent preclinical and clinical studies implicated earlier gestation (Mueller and Bale, 2008; Howerton et al., 2013).

Preclinical studies also demonstrated sex differences (greater in females than males) in a number of domains, including: (1) greater placental glucocorticoid transfer (Montano et al., 1993; Fameli et al., 1994); (2) greater immobility in tasks associated with MDD phenotypic behavior (Alonso et al., 2000); (3) increased ACTH, corticosterone, and glucocorticoid receptor binding (Weinstock et al., 1992; McCormick et al., 1995; Regan et al., 2004); (4) increased corticosterone sensitivity (Rhodes and Rubin, 1999); (5) greater susceptibility to changes following loss of GABA_B receptor function (McClellan et al., 2010; Stratton et al., 2011); (6) greater susceptibility to cell death in AMYG following developmental exposure to dexamethasone (Zuloaga et al., 2011); and (8) greater susceptibility to diet-induced hepatosteatosis and insulin growth factor-1 deficits (Carbone et al., 2012). In humans, at the level of the brain, there have been fewer studies of sex differences in MDD, although some reported decreased HIPP and increased AMYG volumes, greater in females than males (Vakili et al., 2000; Janssen et al., 2004; Weniger et al., 2006). Collectively, preclinical studies support the hypothesis that prenatal exposures (particularly those implicating stress circuitry pathways) facilitate altered programming of stress-related endocrine and neural circuits implicated in the sex-dependent development of depressive-like behavior. Although parallel studies in humans are still in their infancy, we and others are currently testing the hypothesis that prenatal maternal disruption of stress-immune pathways will, in the context of genetic background, result in vulnerability for the sex-dependent risk for MDD in the offspring (Handa et al., 1994; Majdic and Tobet, 2011).

CONCLUSIONS

The number one cause of disability worldwide is MDD, and women are two times the risk of men. This represents ~350 million people worldwide, approximately 16 million in the U.S. alone (WHO October 2012 Fact Sheet). Depression is comorbid with many chronic diseases that are also associated sex differences in risk (Goldstein et al., 2011, 2013). Thus, depression is a major public health problem with substantial economic, social and disease burden that, we argue, requires a sex-dependent lens to understand its pathophysiology. There are key naturalistic opportunities for the study of this higher risk in women, and that is when the brain is differentially flooded with or depleted of gonadal hormones, i.e., fetal development, puberty, pregnancy, and perimenopausal-menopause transition. The evidence briefly discussed here supports the hypothesis that the etiology of sex differences in MDD begins in fetal development and emerges post-puberty. Its onset can be catalyzed by pregnancy (postpartum depression) and the menopausal transition (when there is an increase in MDD onset). The fact that these particular periods during the lifespan have significant implications for MDD onset is consistent with an important role for steroid hormones in MDD. This underscores the importance of promoting further inquiry into the development of adjunctive neuroendocrine treatments, dependent on timing across the lifespan. This lifespan approach to studying sex differences in disorders, like depression, also illustrates how maternal health (e.g., pregnancy), women's mental health, and sex differences in disorders of the brain are linked. Thus, we have argued the importance for preclinical and clinical neuroscience to incorporate a sex-dependent and/or sex-specific lens on investigations ranging from the cellular-molecular level to circuitry, systems, and behavior, an argument that recently was underscored by the new directive from NIH to incorporate this perspective in designs of preclinical studies (Clayton and Collins, 2014). We believe this will provide the basis for the development of sex-dependent therapeutics which will enhance progress to greater efficacy.

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